# The Pharmaceutical Challenge of Cancer Research

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# Formulation Unit

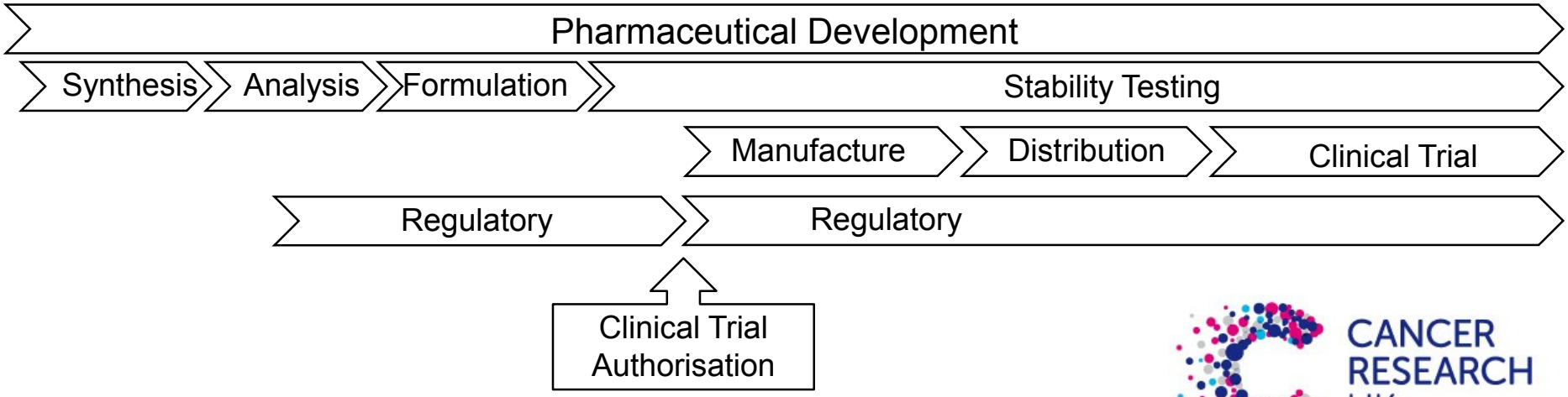
- Remit

  To develop novel anti-cancer drugs selected by Cancer Research UK New Agents Committee for Phase I and II Clinical Trial

  Pharmaceutical Translation Research

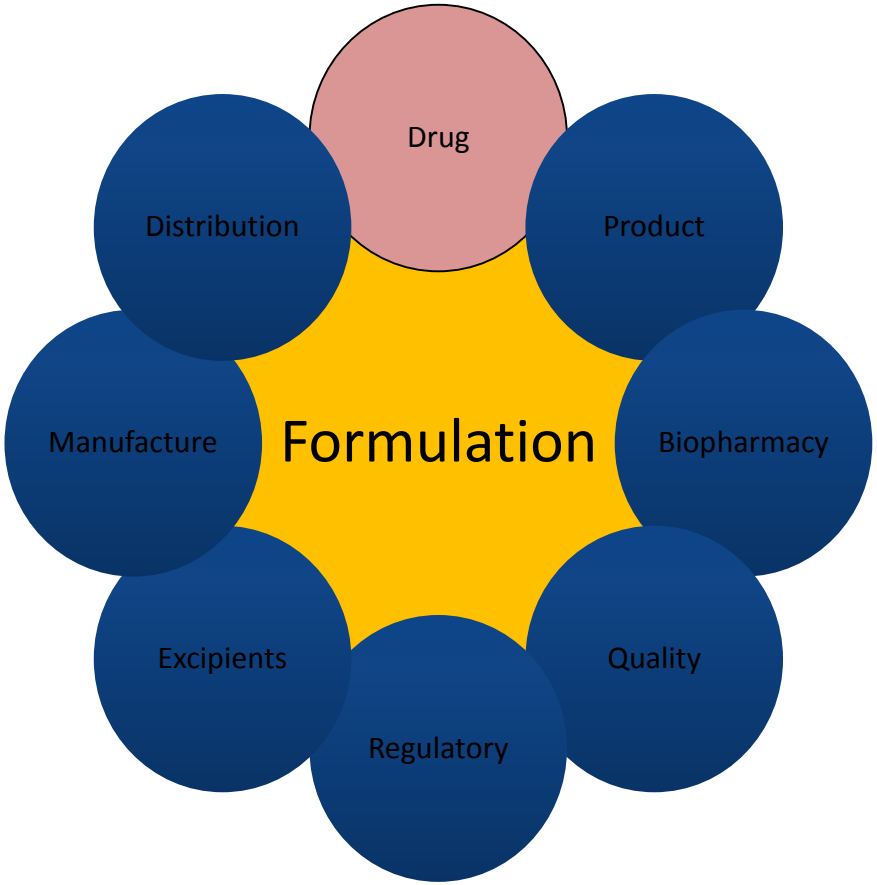
- Established in 1983

  Bench to Bedside – Powder to Product – Molecule to Medicine



# Formulation

- Multiple factors
- One goal
- Limited
  - Knowledge
  - Resource
  - Time

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Science

- Early Projects
- Research Advances
- Recent Projects
- Currents Trends
- Potential Answers

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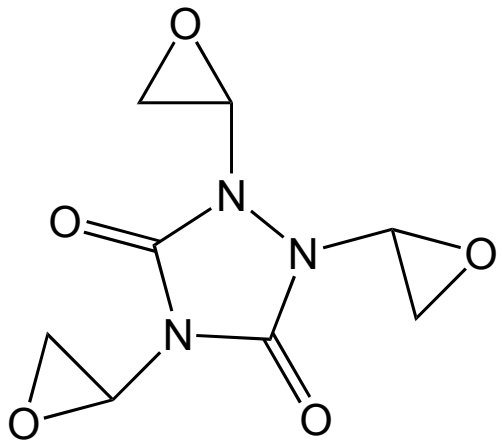
# Early Example - 1984

- 1, 2, 4-triglycidyl urazol - Limited solubility & stability

- Reconstitution Fluid

  Switch from dextrose to NaCl




Cancer Chemother Pharmacol (1984) 12: 198–200

Cancer Chemotherapy and Pharmacology


**The analysis and animal pharmacokinetics of 1,2,4, triglycidyl urazol using a high-pressure liquid chromatographic technique**

**J. Welsh[1], J. F. B. Stuart[1,2], A. Setanoians[1], R. G. G. Blackie[1], P. Billiaert[1,2], G. Halbert[1], and K. C. Calman[1]**

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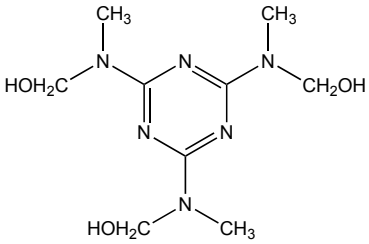
[2] Department of Pharmaceutics, University of Strathclyde, Glasgow, Scotland

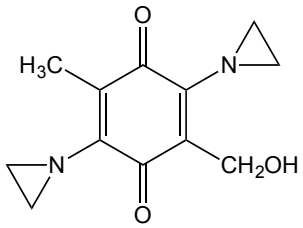
# Early Projects

- Many and varied

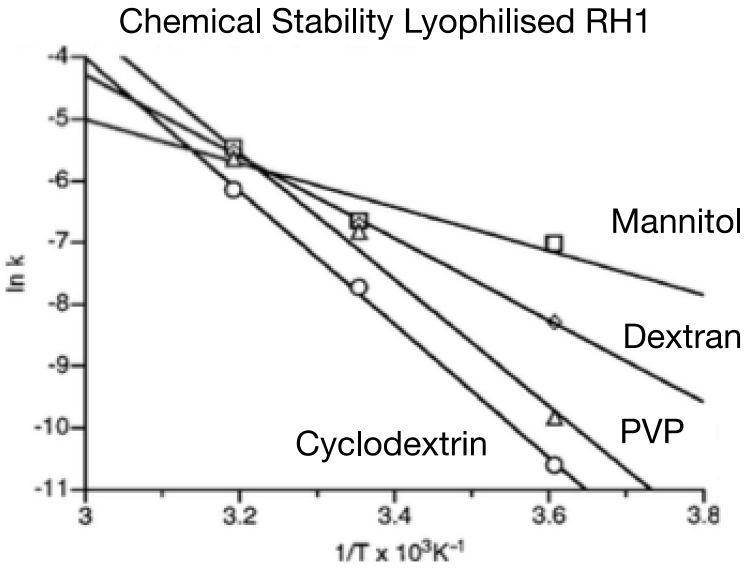
  Exact number unknown
- Small molecules



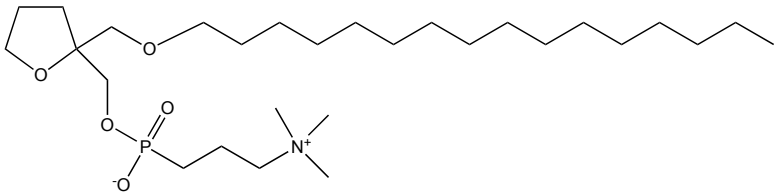

Trimelamol




RH1




Limonene




SRI 62 834

# Clinical Trials

- 1, 2, 4-triglycidyl urazol
- Starting Dose

  30mg/$m^2$ escalated to 900mg/m
- Toxicity
  - Myelosuppression , nausea, vomiting, phlebitis

- RH1
- Eligibility criteria

  Proven cancer, refractory to treatment, no conventional therapy, >18 yrs, life expectancy >3 months

| Tumour Type | No |
|---|---|
| Colorectal | 8 |
| Gastric | 3 |
| NSCLC | 2 |
| Melanoma | 2 |
| Merkel cell carcinoma | 1 |
| Pancreatic | 1 |
| Renal | 1 |

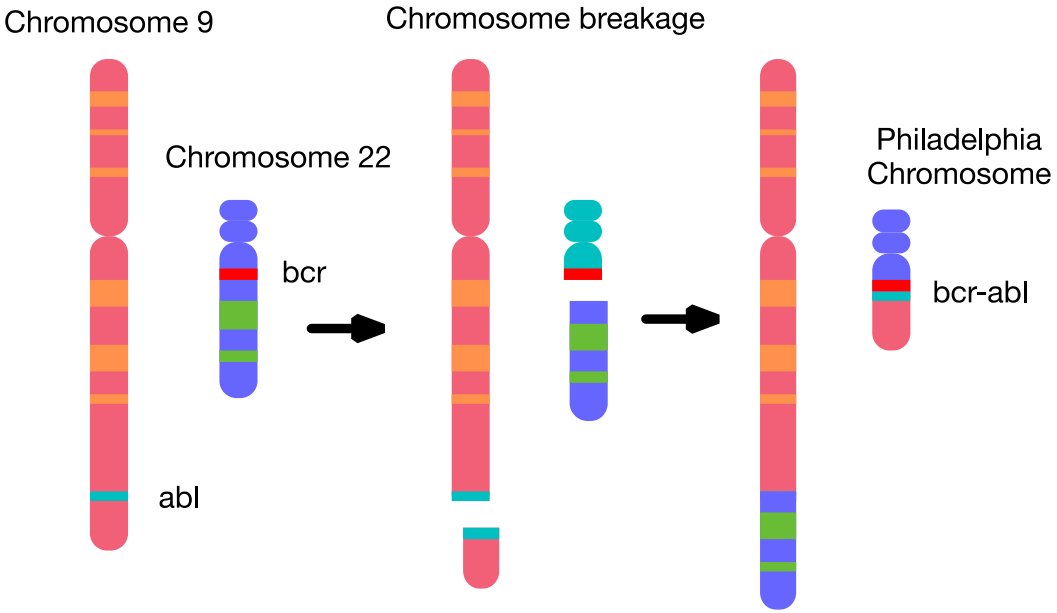
# Common Issues

- Pharmacology
  - Cytotoxic chemotherapy
  - Limited administration
- Majority of formulations injections
- Drug solubility
  - Range of formulation techniques applied
- Drug stability
  - Hydrolytic – lyophilisation
  - Non-hydrolytic – physicochemistry
- General trials

# Research Advances

- Imatinib – 2001

  "Dawn of targeted treatments"

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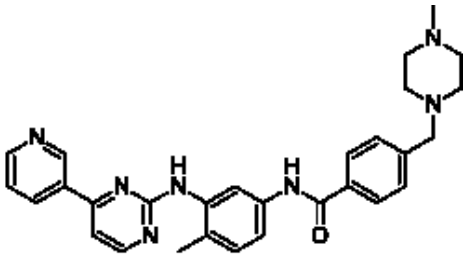
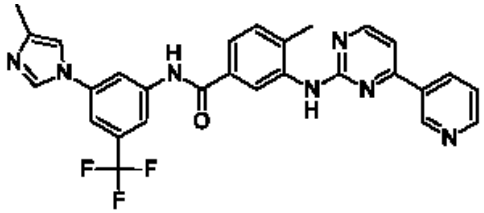
# Very Different Drugs

imatinib



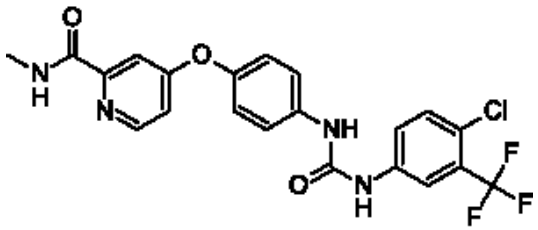
Solubility 200mg/ml
Oral Bioavailability 98%

nilotinib



Solubility sparingly
Oral Bioavailability 31%

sorafenib



Solubility (1:2 DMSO:PBS) 0.3mg/ml
Oral Bioavailability 50%

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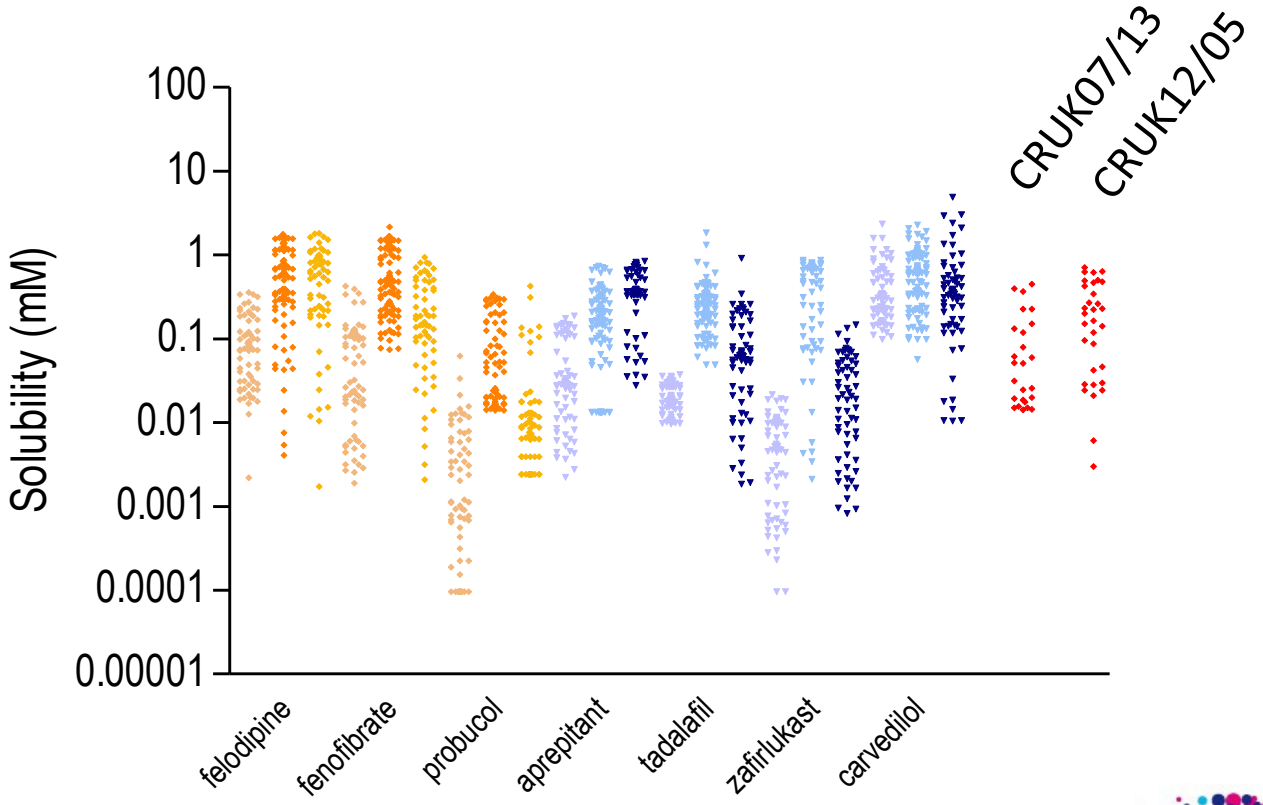
# Intestinal Solubility Variation

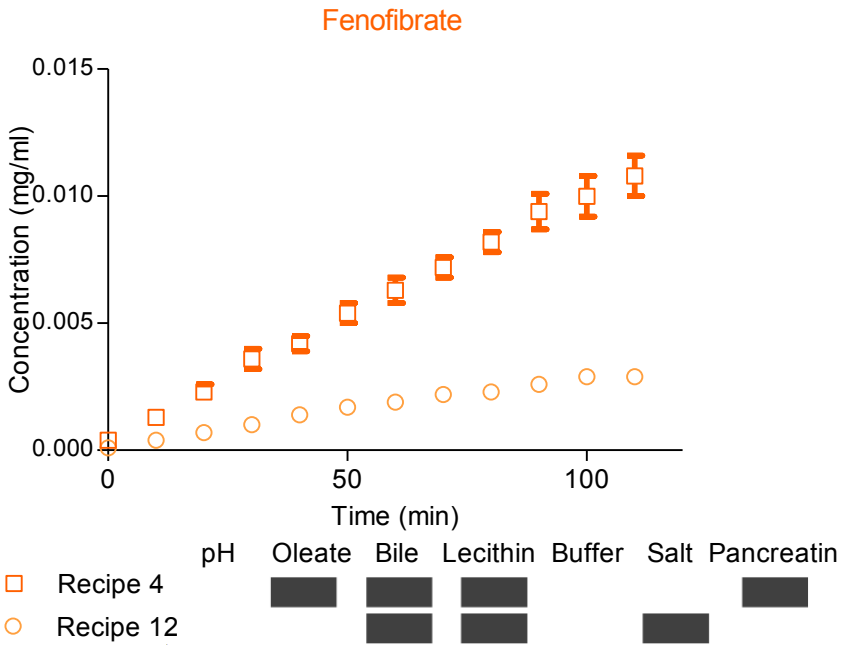
- Impact of simulated gastrointestinal fluid composition



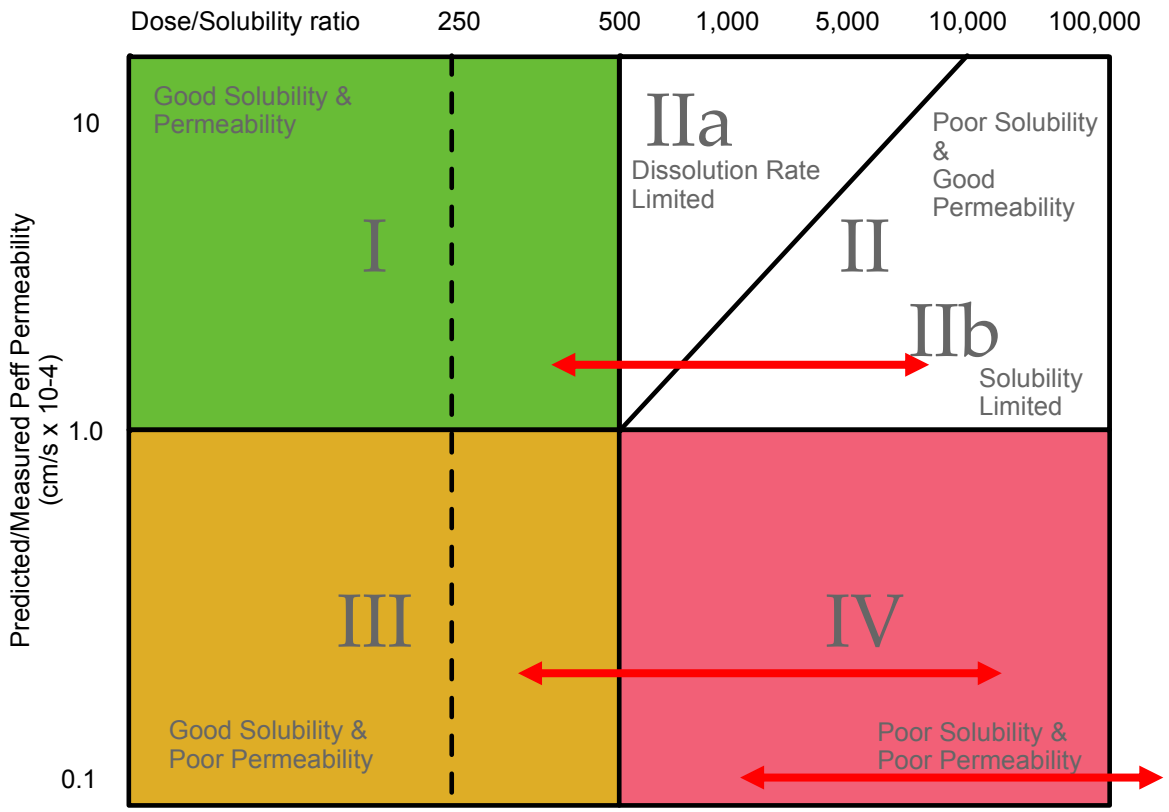

Khadra, I., et.al., (2015) Eur. J. Pharm. Sci., 67: 65-75 (Fasted data only)

# Impact on Dissolution

- Low solubility
  - Slower dissolution
- Natural GIT variation
- Not applicable
  - Amorphous
  - Bioenhanced
  - But does it stay in solution?

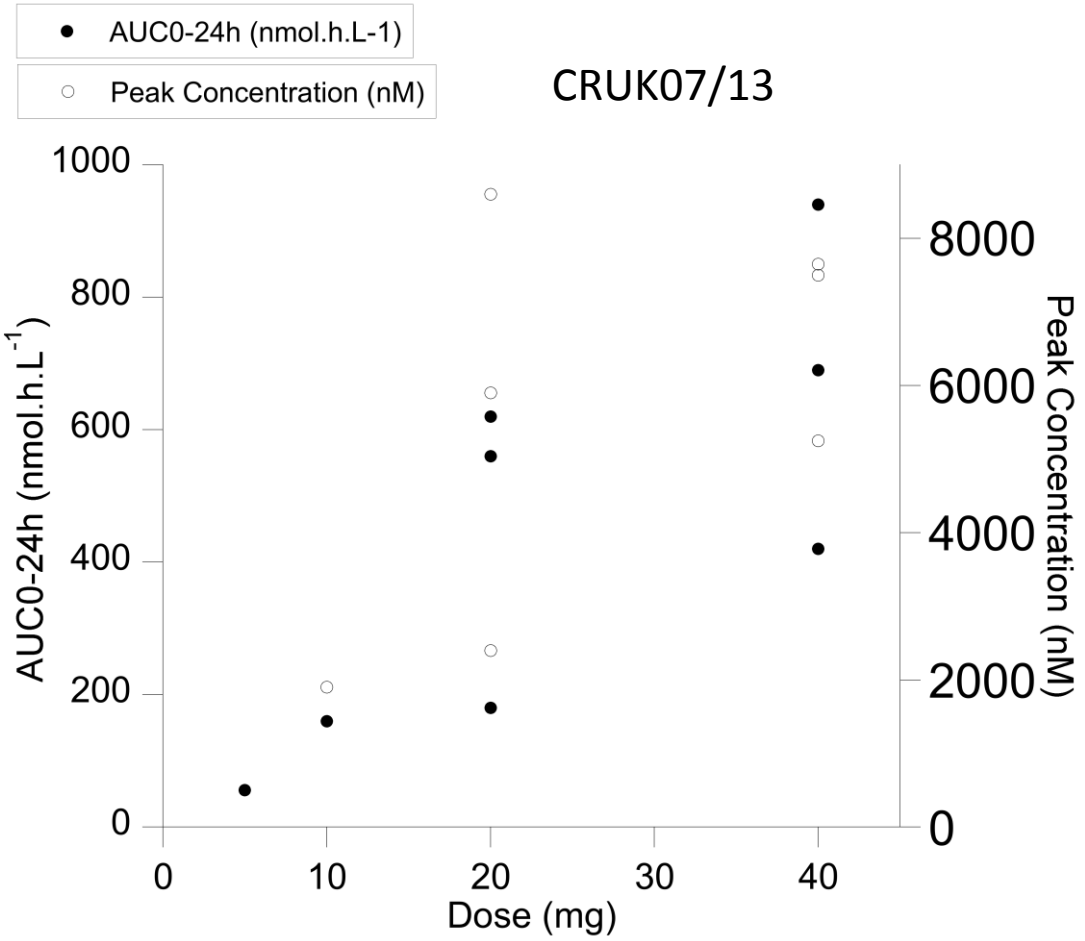


# Biopharmaceutics Classification System



# Impact on pharmacokinetics

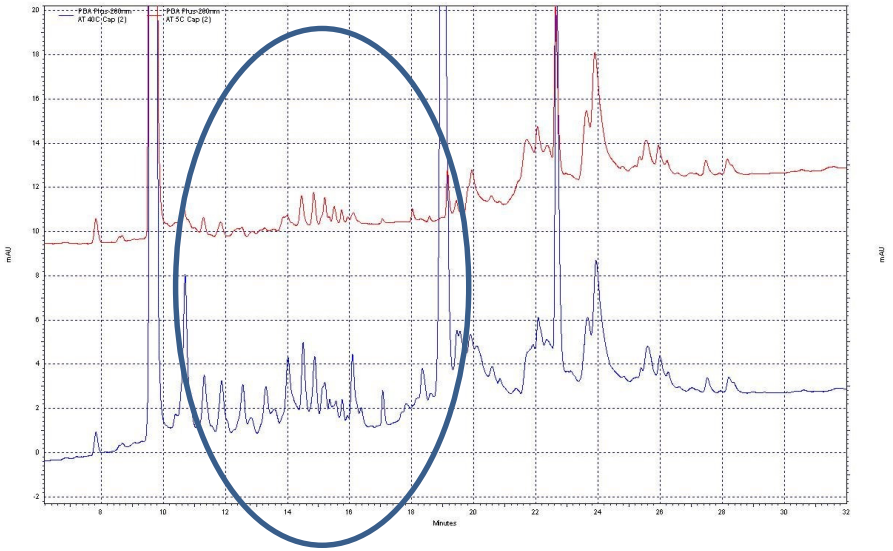
- Phase 1 Dose escalation studies – BCS I to BCS II




Impacts receptor exposure

# Bioenhanced Formulations

- Improve dissolution
  - Amorphous
  - Solid solutions
- Spring and parachute effect
- Stability
  - Chemical & Physical
- Solid solution
  - Drug/Excipient
  - Intimate contact
- Excipient Quality



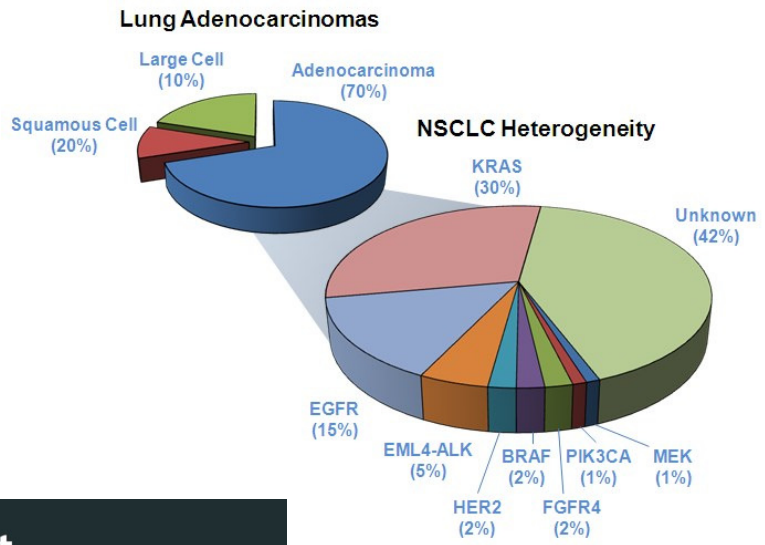
# Common Issues

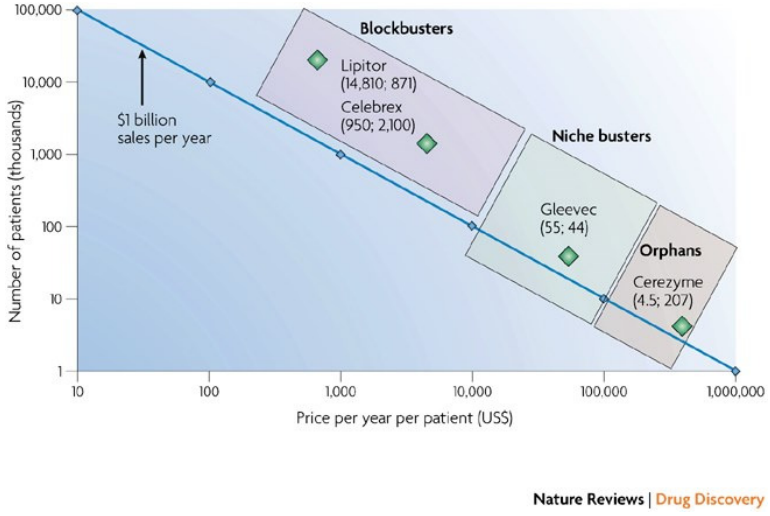
- Pharmacology
  - Targeted chemotherapy
    - Single pathway
  - Continuous administration
- Majority of formulations oral
- Drug solubility – impacts on drug absorption
- Bioenhanced formulations
  - Stability problems
- Targeted trials

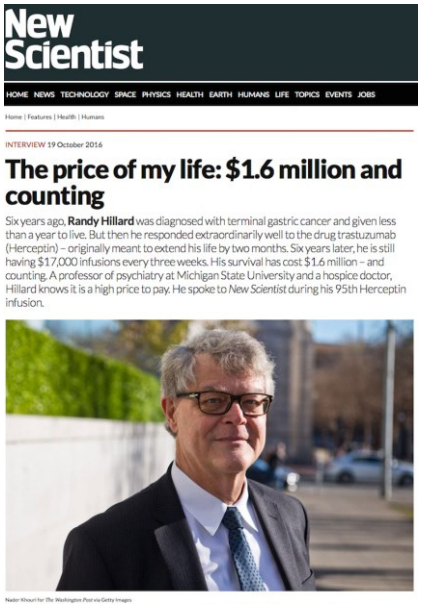
# Current Trends I

- Smaller patient numbers
- Therapy cost increases
- Combination therapies
- Agile therapy

  Rapid changes





New Scientist

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INTERVIEW 19 October 2016

**The price of my life: $1.6 million and counting**

Six years ago, **Randy Hillard** was diagnosed with terminal gastric cancer and given less than a year to live. But then he responded extraordinarily well to the drug trastuzumab (Herceptin) – originally meant to extend his life by two months. Six years later, he is still having $17,000 infusions every three weeks. His survival has cost $1.6 million – and counting. A professor of psychiatry at Michigan State University and a hospice doctor, Hillard knows it is a high price to pay. He spoke to *New Scientist* during his 95th Herceptin infusion.



Nader Khouri for *The Washington Post* via Getty Images

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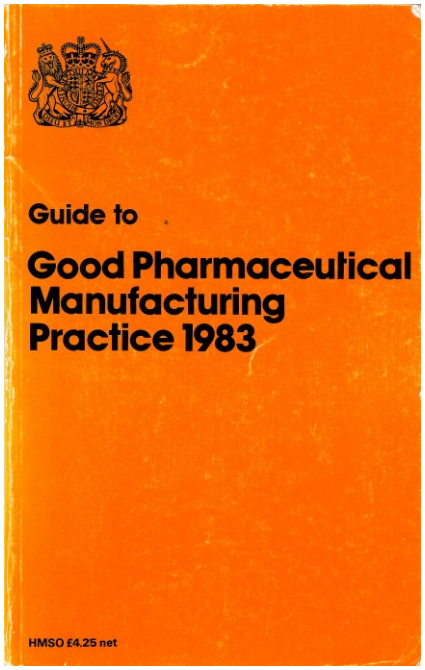
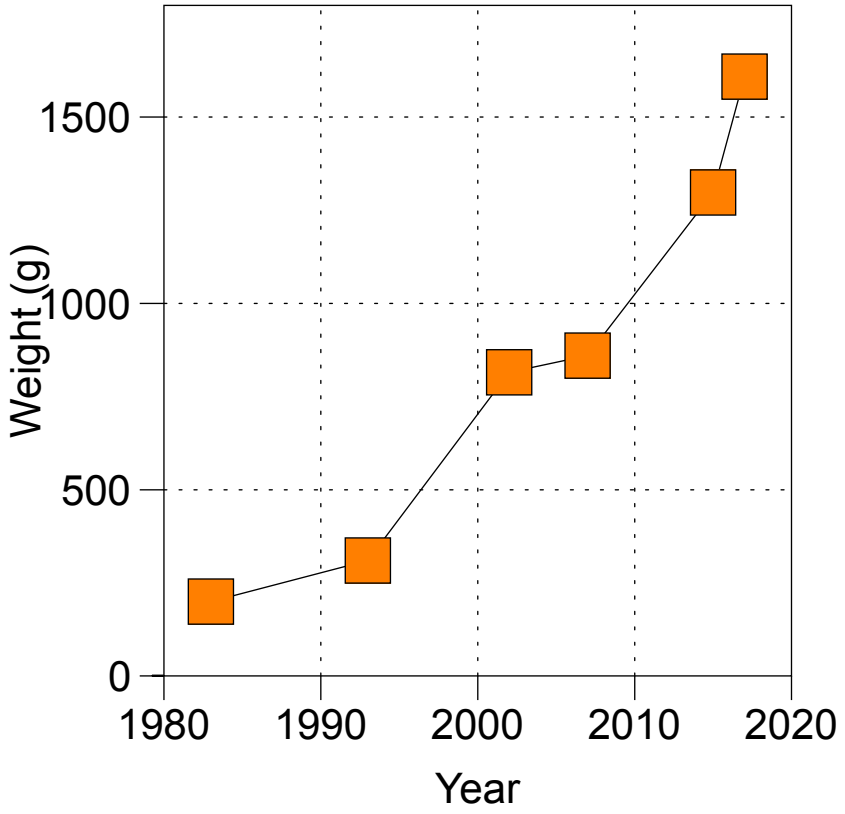
# Current Trends II




Pharmaceutical Hockey Stick

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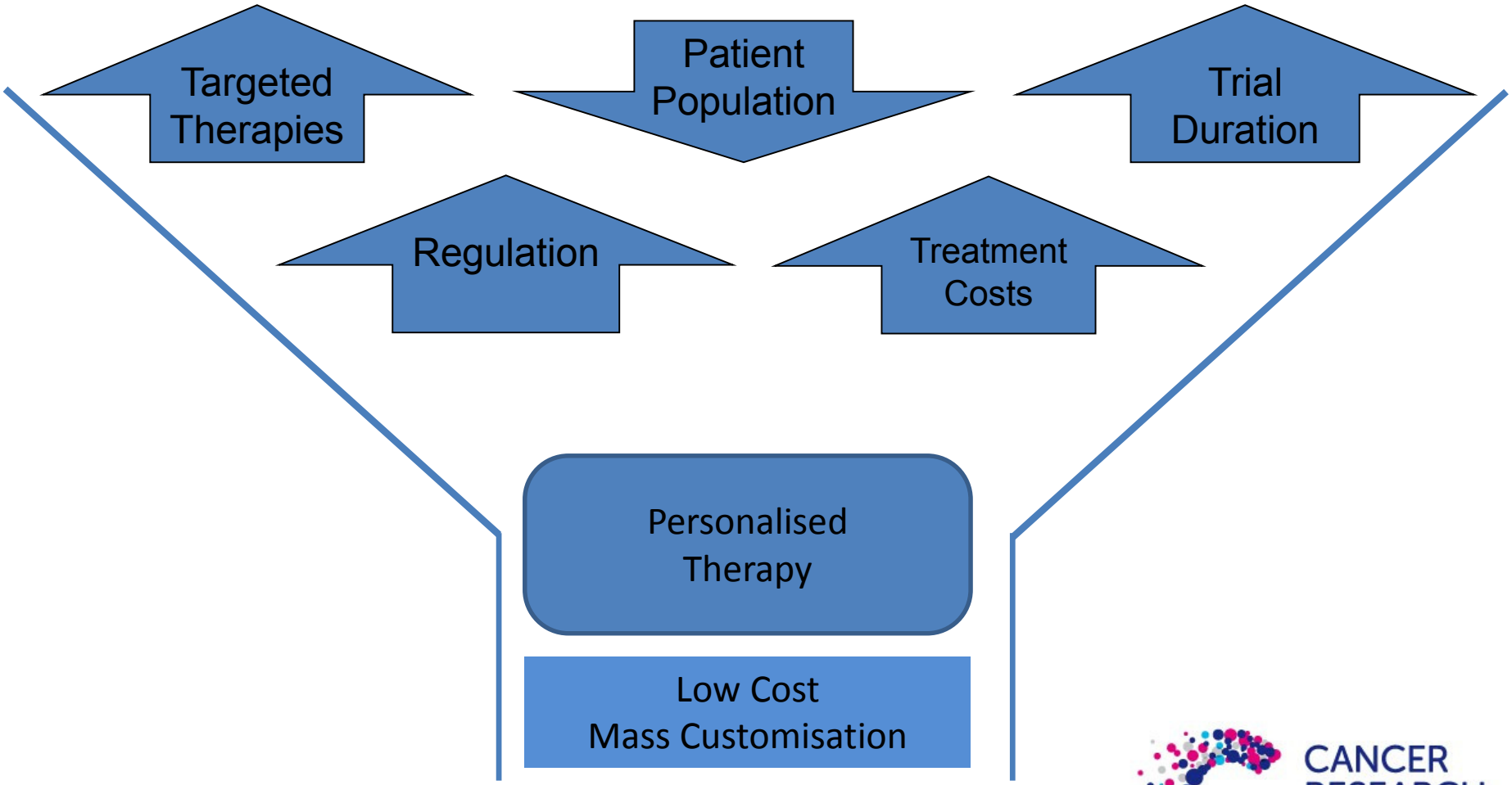


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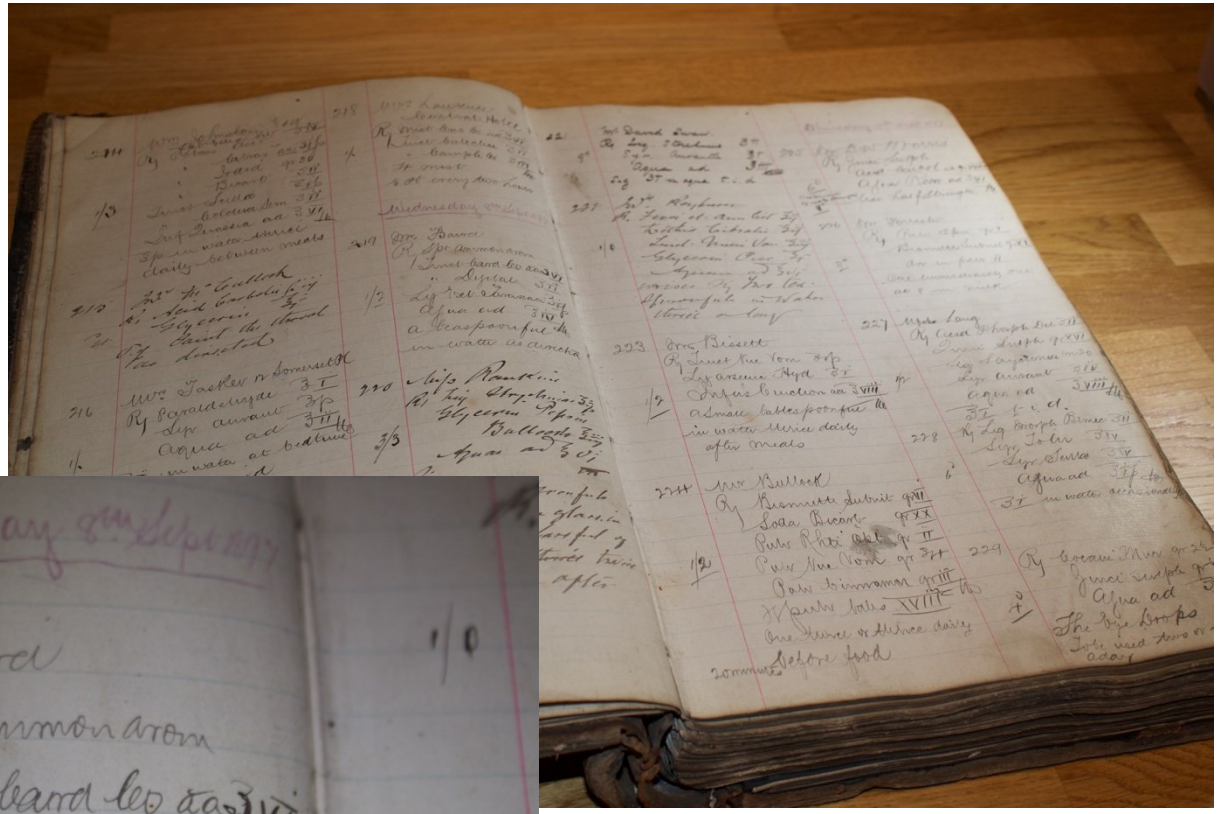
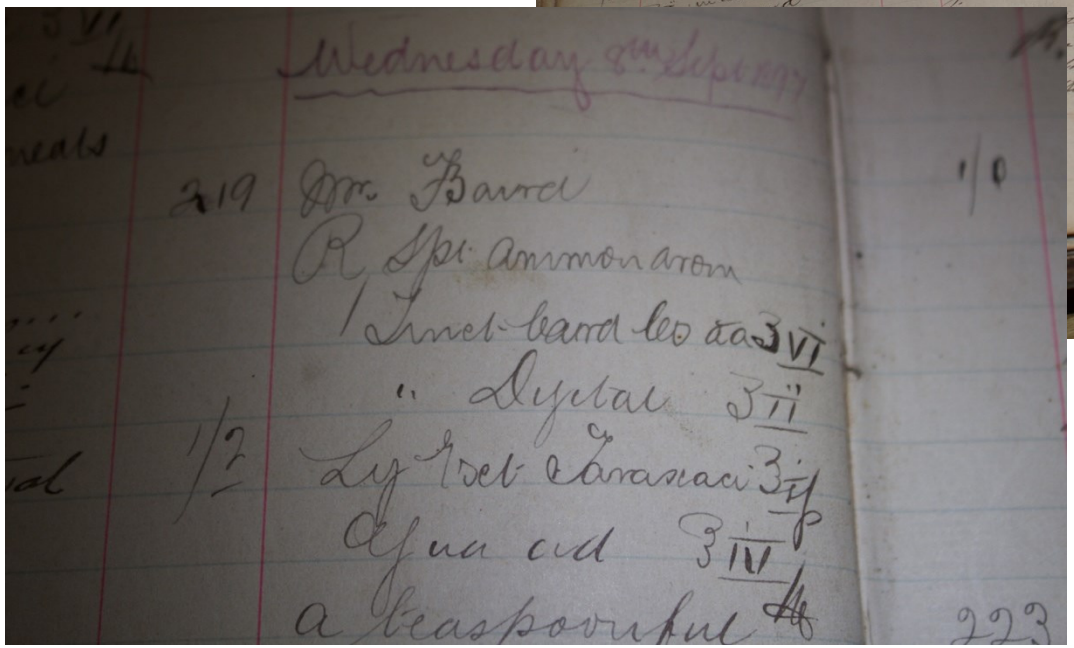
# Mass Customisation

- This is not new!



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# Future Pharmaceutical Challenge

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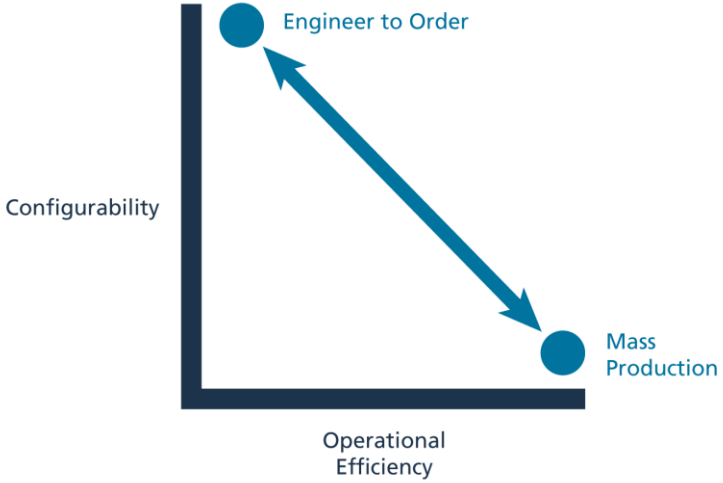
Solutions – scaleable, quick, agile, low cost, GMP compliant, patient friendly

Does one formulation and manufacturing technology fit all?

Are there other aspects that can change?

Basic and applied research required




3D Printing
Just in time manufacture
Small scale development
Individual patient trials

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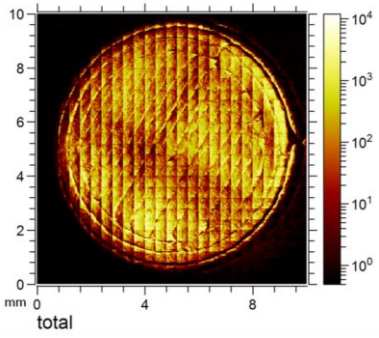
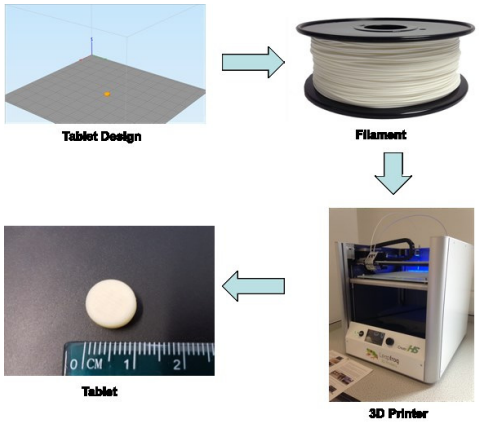
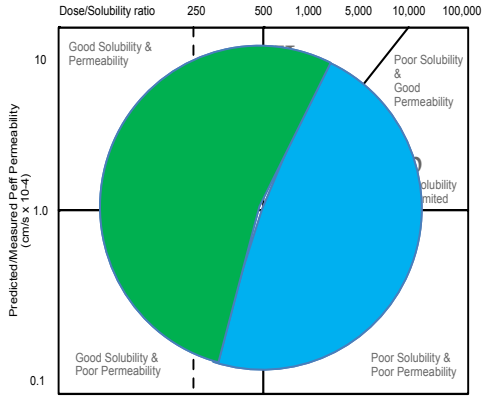
# 3D Printing & Injection Moulding

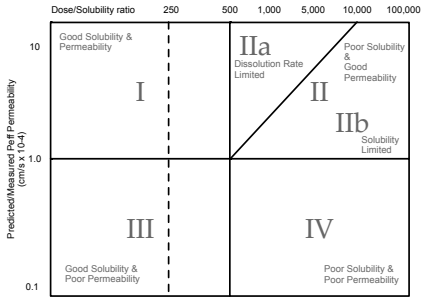
- Hot topic – a la mode
  - Multiple groups UK and world-wide - multiple approaches
- Marketed product
  - New field
- Multiple areas of research
  - Equipment, process, parameters, formulation, product
- Future
  - Wide open

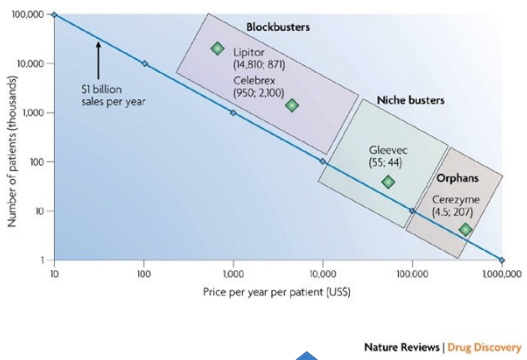


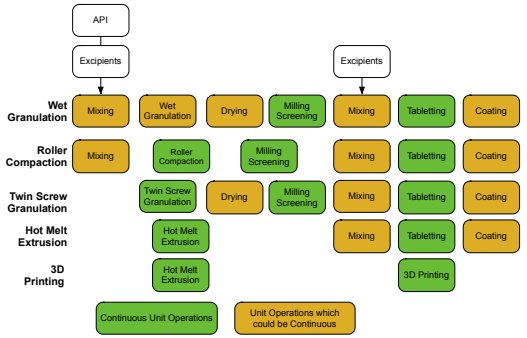



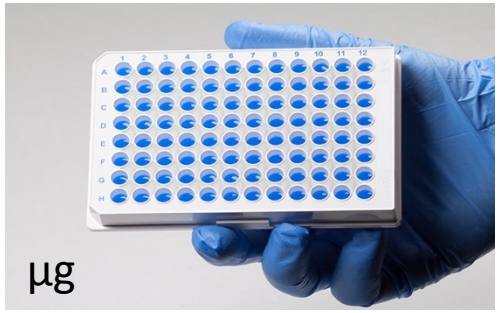
# Predictive Pharmaceutics




Predict, Integrate, Design, Test

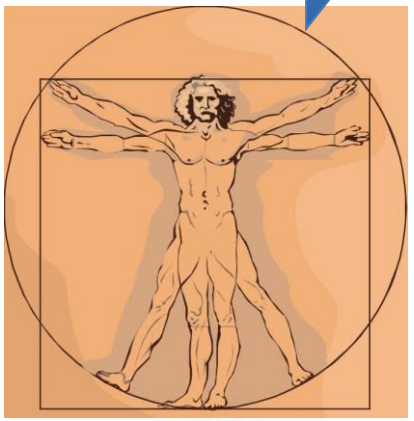


µg

Discovery

mg

Development



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Treatment

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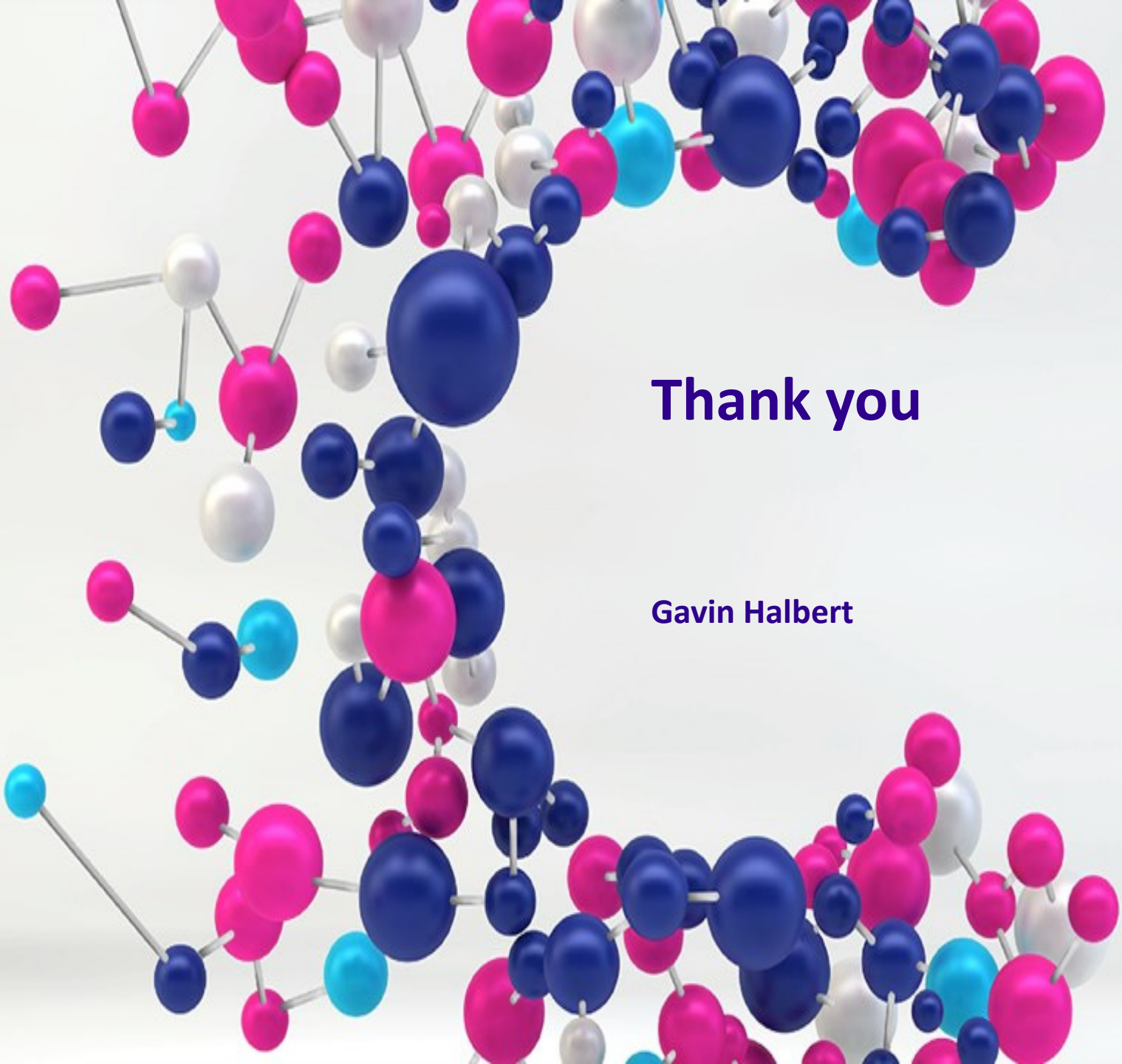
# Acknowledgements


- You for listening
- Collaborators
  - Many and varied
    - Local, national and international
- Cancer Research UK Funding
  - EPSRC, EU FP7, MRC



# Thank you

Gavin Halbert